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REVIEW ARTICLE

Special Considerations in Breast Cancer Risk and Survival

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Experimental and clinical evidence suggests that breast neoplasia appears to be a hormone-dependent process that may also be influenced by dietary factors in many women. Conflicting reports on the relationship between exogenous hormones and the development, progression, and recurrence of breast cancer are critically examined in this report. The absolute breast cancer risk associated with either hormone replacement therapy or oral contraceptive use has not been clearly defined. Data from some large prospective studies have actually documented lower mortality rates for women taking hormone replacement compared with those for women who did not have hormone replacement therapy. In this regard, age, duration of use, and preexisting breast cancer risk factors must be taken into account. Although the results of two major prospective clinical trials addressing the role of timing of surgery within the menstrual cycle are forthcoming, the majority of studies have found no consistent association between timing of surgery and breast cancer survival. Recently reported prospective randomized data showing that selective-estrogen-receptor-modulators can act as effective chemoprevention agents in women at increased risk for breast cancer development are presented. Finally, information regarding the effect of dietary manipulation on breast cancer risk and survival is reviewed.

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KEY WORDS: hormone replacement therapy; estrogen; timing of breast cancer surgery

INTRODUCTION

Progress in breast cancer research is proceeding at a rapid pace, and the results are impressive. We are finally seeing an overall decrease in breast cancer mortality rates among women in the United States [1], and effective agents for chemoprevention as well as adjuvant therapy are now a reality.

Nonetheless, the very high incidence of breast cancer, expected to afflict one in nine American women, signifies that this is still a disease that poses a major threat to the productivity and well-being of every woman. It is, therefore, imperative that we continue to investigate the potential carcinogenic effects associated with exposure to various environmental and medicinal substances. The substances most commonly implicated in breast cancer risk are exogenous hormones and dietary components. Extrapolation of data from the exogenous hormone controversy leads to a discussion regarding the potential oncogenic effects of timing breast surgery based on the

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hormonal fluctuations of the menstrual cycle. In this review, we will discuss the data pertaining to the following special considerations in breast cancer risk and survival:

1. exogenous hormones
   a. oral contraceptives (OC)
   b. hormone replacement therapy (HRT), defined as combined estrogen and progesterone replacement, or estrogen replacement therapy (ERT)
2. timing of surgery based on the menstrual cycle
3. nutritional factors

EXOGENOUS HORMONES

Background

The controversy behind exogenous hormone use and breast cancer risk is predicated on the concept of breast neoplasia as a hormone-dependent process. The ability to control breast cancer with hormonal manipulation has been recognized since 1896, when Beatson reported on oophorectomy as successful treatment for this disease [2]. Since that time, several other epidemiologic and scientific lines of evidence have developed that also support this concept.

It is well known that menstrual factors resulting in exposure of the breast to increased numbers of estrogen/ovulatory cycles over a lifetime (such as early menarche, late menopause, and nulliparity) can increase risk of breast cancer [3]. Conversely, bilateral oophorectomy prior to age 40 may reduce breast cancer risk by as much as 50%, and interruptions of the menstrual cycle in the form of multiple pregnancies may confer a protective effect. The impact of pregnancy is strongest for first pregnancy occurring at a young age. The normally high rate of post-pubertal ductal epithelium proliferation is transformed into the process of terminal ductal and lobular stem cell differentiation because of the hormonal influence of pregnancy, theoretically rendering the breast more resistant to carcinogenesis [4,5]. Henderson et al. [6] hypothesized that completion of a full-term pregnancy is crucial for this protective effect, as the rapid increase in free estradiol during the first trimester of pregnancy is "equivalent to several ovulatory cycles over a relatively short period of time"; they further suggested that failure to override this estrogenic surge with the subsequent hormonal changes of advanced pregnancy (as occurs with first trimester abortions) can increase breast cancer risk. It is also well known that estrogen and progesterone exert proliferative effects on human breast tissue [7,8] and that estrogen can promote mammary tumorigenesis in animal models as well as in tissue cultures in vitro [4,9].

Postmenopausal obesity has been associated with increased breast cancer risk, and this appears to be mediated by age-related variations in estrogen metabolism. In the postmenopausal woman, androstenedione, synthesized in the adrenal gland, is the principal estrogen precursor following decline of ovarian function. Increased conversion of androstenedione to estrone by fat cells, resulting in elevated levels of this predominant postmenopausal estrogen, is reputed to be the underlying explanation for the increased breast cancer risk seen in obese postmenopausal women [4,10]. Simarlarly, male breast cancer is also likely to be related to factors resulting in abnormalities of estrogen metabolism, such as liver disease or genetic defects [11]. In contrast, for premenopausal obese women, derangements of the estrogen-progesterone balance and subsequent menstrual disturbances result in a decreased breast cancer risk [7].

Finally, several studies have demonstrated that serum hormone levels and mammary estrogen receptor content of non-cancer patients may be associated with an increased risk of developing breast cancer. In two prospective studies conducted in the United States, Dorgan et al. [12] and Toniolo et al. [13] demonstrated a correlation between elevated serum estrogen and testosterone levels and subsequent risk of developing breast cancer among cohorts of postmenopausal patients. Berrino et al. [14] demonstrated similar findings for a cohort of postmenopausal women from Italy. Bernstein et al. [15] found a correlation between serum estradiol levels and breast cancer incidence between premenopausal women in Los Angeles and Shanghai. The data is strongest for postmenopausal patients, and a recent evaluation of plasma estrogen levels and breast cancer risk among postmenopausal participants of the Nurses Health Study confirms this correlation [16]. It is important to note, however, that there can be significant interlaboratory variability in hormone level assays, and this may be particularly true when samples from postmenopausal patients, in whom the levels are already at the lower end of the measureable spectrum, are analyzed. Khan et al. [17] and Ricketts et al. [18] demonstrated that although estrogen receptor content of normal breast tissue is lower than that of cancerous tissue, it is measurable and may be related to risk of breast cancer. It has also been suggested [18] that levels of estrogen receptor expression could be useful in selecting patients for chemoprevention studies or determining relative safety of HRT.

Oral Contraceptives

Oral contraceptives (OC) have been marketed extensively over the past 30 to 40 years; worldwide use is estimated at over two hundred million women, and in the United States it is projected that approximately 80% of all women will have used OC at some time in their life by the age of forty [19]. Studies evaluating a possible association between OC and breast cancer risk have been hampered by changes in composition of OC over time and because of individual patient variation in duration of use.

Early evidence that OC could in fact significantly in-

TABLE I. Oral Contraceptives and Breast Cancer Risk*

Study	No. of patients	Age Dx	Years of use	Relative risk
Pike et al., 1983 [20]	314P	<37	≥6	4.9
	314C			
CDC-CASH, 1983 [21]	689P	<55	≥11	0.9
	1,077C			
Stadel et al., 1985 [22]	2,088P	<45	>4	1.1
	2,065C			
Miller et al., 1986 [23]	521P	<45	3–4	0.8
	521C		>7	1.4
Jick et al., 1989 [24]	127P	<43	<5	0.7
	174C		≥10	1.4
Romieu et al., 1989 [25]	>118K	<65	<1	1.2
	Cohort		≥3	0.9
Weinstein et al., 1991 [26]	326P	<50	1–4	1.3
	323C		>4	1.8
Wingo et al., 1991 [27]	524P	<35	1–2	1.5
	704C		8–10	1.3

*P = numbers of patients; C = number of controls; K = thousand.

crease risk of breast cancer was reported by Pike et al. [20] in 1983. In this case-control study, 314 patients with breast cancer who were less than 37 years of age at time of diagnosis were matched to 314 controls. Use of OC with a high progesterone content for more than 6 years starting at under age 25 was associated with a relative risk of 4.9 for breast cancer development. Since that time, several studies have been conducted in the United States to quantify the level of risk for breast cancer conferred by OC. The results of some of these studies are summarized in Table I [20–27]. Most studies [20–24, 26,27] have been case-control projects; these reports retrospectively evaluate rates of OC use among groups of patients with breast cancer and compare them with rates of OC use among matched groups of patients without cancer. The results are rather inconsistent: some studies demonstrate some increased risk of breast cancer associated with OC use, and others demonstrate a protective effect associated with OC use. It should be noted that in most studies, the relative risk estimate is close to unity, indicating that whichever effect OCs have (if any), it is probably fairly modest in magnitude. However, the high incidence of breast cancer in the United States suggests that even small increases in relative risk could translate into many more cases of breast cancer.

One of the most widely quoted case-control studies on OC and breast cancer was the Center for Disease Control's Cancer and Steroid Hormone (CASH) Study [21]. This project, first reported in 1983, evaluated 689 patients diagnosed with breast cancer between the ages of 20 and 54, who were identified through the Surveillance, Epidemiology and End Results (SEER) Program. These patients were matched to 1,077 controls, and on initial analysis there was a lesser risk of breast cancer for women who had been users of OC compared to those who never used OC (relative risk 0.9). Results of the CASH study were reevaluated and reported in 1991 by Wingo et al. [27], and in this review a particular focus was placed on the issue of OC exerting variable, age-related associations with breast cancer risk. This analysis revealed a trend toward increased risk for OC users under the age of 35 (relative risk, 1.4), and a slight decrease in risk for OC users in the 45 to 54 years old (relative risk, 0.9).

The Nurses' Health Study [25], which will be discussed in more detail in the section reviewing HRT, provides some data regarding relative risk of breast cancer among OC users followed in a prospective fashion. In the 1986 report on a cohort of more than 1000,000 nurses with more than one million person-years of follow-up, no significant increase in breast cancer risk could be identified in association with OC use. This relative risk was not affected appreciably by duration of use, history of fibrocystic breasts, or family history of breast cancer.

In 1996, a meta-analysis of 54 epidemiologic studies of OC and breast cancer was published in the *Lancet* [28]; this review compiled data on more than fifty-three thousand breast cancer patients and more than 100,000 control subjects from 25 countries. For current users of OC, a small but statistically significant increased risk of breast cancer was seen (relative risk, 1.24; $2P < 0.00001$), and risk was somewhat increased for 10 years following discontinuation of OC. The tumors detected in OC users were also found to be earlier stage lesions than those that were detected in non-OC users. One explanation of these findings is related to the concept of estrogen acting as a promoter rather than a cause of the neoplastic process. Under this circumstance, it would be expected that more tumors would be detected during and following OC use, because the estrogen content would merely be expediting the clinical appearance of a preexisting but previously occult tumor. A second explanation of the study results is that women who are OC users are necessarily receiving healthcare follow-up, which presumably includes surveillance for breast cancer.

HORMONE REPLACEMENT THERAPY

Background

The controversy surrounding HRT and breast cancer is complicated by the prevalence of breast cancer and by the fact that we live in an aging society. The health risks associated with the postmenopausal estrogen-deficient state, namely cardiovascular disease and osteoporosis, are being faced by increasing numbers of women who are still in the prime years of their professional and domestic lives. Approximately one quarter of the American population is currently over the age of 55, and cardiovascular disease is the leading cause of death for postmenopausal women. Cardiovascular disease accounts for nearly three times as many deaths as cancer among women over the age of 65 [29]. Osteoporosis afflicts approximately 25 million Americans, and it is estimated that one half of

TABLE II. Hormone Replacement Therapy: Breast Cancer Risk in the General Population

Study	Year	Number of women	Mean number of years follow-up	Relative risk
Hoover et al. [43]	1976	1,891	12	1.3
Gambrell et al. [44]	1983	5,563	7	0.4
Hunt et al. [45]	1987	4,544	6	1.59
Bergkvist et al. [46]	1989	23,244	5.7	1.1
Mills et al. [47]	1989	20,341	6	1.7
Colditz et al. [48]	1995	23,965	16	1.32

women will experience an osteoporotic fracture by the age of 75. In particular, hip fractures are a major problem; they are associated with a 34% mortality rate within 6 months, and the corresponding health care costs are several billion dollars annually [30].

Menopause also causes several other symptoms that have a significant adverse impact on quality of life. Vasomotor symptoms are experienced by 80% of menopausal women; urinary incontinence, vaginal dryness, sleep disturbances, depression, anxiety, and memory losses are being reported increasingly and have all been related to changes in estrogen [29,31–33].

General Population

Estrogen replacement therapy (ERT) in postmenopausal women has been well proven to reverse several risk factors for cardiovascular disease, such as low HDL cholesterol levels [34], and ERT has been associated with a 40 to 60% reduction in rates of complications of cardiovascular disease such as myocardial infarction and sudden death [29,35–37]. ERT also reduces rates of bone resorption, thereby reversing rates of osteoporosis and osteoporotic fractures, by as much as 60% [29,38,39]. Unfortunately, ERT exerts a dose- and duration-of-use-dependent proliferative effect on the uterine lining and several studies have demonstrated an increased rate of endometrial cancer associated with ERT [29,37,40–42]. Results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, however demonstrated that addition of cyclic micronized progesterone to ERT negated the risk of endometrial hyperplasia (as measured by baseline and annual endometrial aspiration biopsy) without adversely affecting the favorable impact of ERT on the cholesterol profile [34].

The effect of ERT on risk of breast cancer remains an unresolved issue. To date, no prospective randomized study has been completed, and many of the patterns and inconsistencies demonstrated in the available data are similar to those seen in the OC published series. Table II demonstrates the results of several studies conducted in the United States and abroad. The relative risk estimates [43–48] vary considerably. A protective effect was seen in the Gambrell et al. study [44], where a relative risk of 0.3 was associated with HRT (combined estrogen and progestin) among more than 5,500 women who received following care at the Wilford Hall USAF Medical Center. In this study, the relative risk estimate was calculated by comparing the observed breast cancer incidence to the expected incidence based on SEER data. Mills et al. [47] followed a cohort of over 20,000 Seventh-Day Adventist women and found a relative risk of 1.7 associated with any history of HRT use; this relative risk increased further to 2.5 for current HRT users and to 2.8 for HRT users with a history of benign breast disease. Colditz et al. [48] also found a significant increase in relative risk associated with current HRT use (relative risk, 1.32) in the 1995 report on findings from the Nurses' Health Study. As noted previously, the correlation of current use with increased risk may be related to promotional effects of estrogen on tumorigenesis, or it may be secondary to surveillance.

Updated results of the Nurses' Health Study were published in 1997 [49]. At the time of the report, more than 120,000 registered nurses had completed biennial questionnaires since 1976, and more than 3,600 deaths had been documented. Several important findings were reported. Women who underwent HRT experienced lower mortality rates compared with women who did not have HRT (relative risk of death, 0.63). This benefit of HRT was strongest for women who had preexisting risk factors for atherosclerotic heart disease (e.g., current tobacco use, parental history of premature myocardial infarction, diabetes, or hypertension). For those women considered to be at low risk for cardiac disease, there was a lesser benefit from HRT (relative risk of death, 0.89). After 10 years of HRT, however, mortality rates began to rise, predominantly from an increasing rate of breast cancer-related deaths.

Breast Cancer Survivors

As would be expected, the issues of HRT become even more complicated when its use is considered for women with a known history of breast cancer. This population of postmenopausal breast cancer survivors is rising; statistics from the American College of Surgeons' National Cancer Database [50] reveal that approximately 80% of patients with breast cancer are 50 years of age or older. In addition, the increasing use of adjuvant chemotherapy for patients whose axillary lymph nodes are negative or positive for disease results in an additional population of younger patients who are rendered prematurely menopausal. Data from The University of Texas M.D. Anderson Cancer Center [51] and from Memorial Sloan-Kettering Cancer Center [52] reveal that 60 to 80% of premenopausal patients receiving doxorubicin or methotrexate-based therapy become amenorrheic.

The question of HRT and breast cancer survivors generates a discussion of clinical data implicating endogenous estrogen production with breast cancer outcome.

TABLE III. Hormone Replacement Therapy Among Breast Cancer Survivors*

Study	Year	Number of patients	Therapy	Duration (mos)	Follow-up (mos)	Number of relapses (%)
Stoll and Parbhoo [56]	1988	65	HRT	3–6	24+	0 (0)
DiSaia et al. [57]	1993	77	Varied	27	59	7 (9)
Powles et al. [58]	1993	35	ERT + Tam	14.6	43	2 (6)
Wile et al. [59]	1993	25	HRT	24	24	1 (4)
Dhodapkar et al. [62]	1995	4	ERT	N/A	N/A	N/A
Eden et al. [61]	1995	90	ERT	18	84	7 (7.8)
Vassilopoulou-Sellin et al. [60]	1997	43	ERT	31	144	1 (2.3)

*HRT = combined hormone replacement therapy; ERT = estrogen replacement therapy.

Results from the Early Breast Cancer Trialists' Collaborative Group [53] and other series [54] have demonstrated that ovarian ablation may be associated with a 15 to 25% reduction in rates of breast cancer recurrence and of mortality. This has led to speculation that the ovarian failure induced by chemotherapy may contribute to the survival benefit derived from adjuvant therapy. Additional complicating data was reported by Lonning et al. [55] in a study from Finland wherein rising serum estrogen levels were shown to be inversely related to disease-free interval.

These issues underscore the concerns regarding the impact of exogenous hormones on micrometastatic disease and whether we can safely offer postmenopausal patients with breast cancer the benefits of ERT. Nonetheless, several small studies [56–61] were conducted that appear to indicate that ERT may not significantly increase breast cancer relapse rates. The results of these studies are summarized in Table III. In contrast, there is also a report from the Mayo Clinic [62] on four patients diagnosed with metastatic breast cancer while receiving ERT; in all four patients, withdrawal of the ERT alone resulted in regression of the metastatic disease.

Some of these conflicting findings should be clarified by the prospective, randomized clinical study currently under way at M.D. Anderson Cancer Center. Vassilopoulou-Sellin and Theriault [63] are studying women with a history of stage I or stage II breast cancer who are now receiving follow-up care. Eligible patients must have had a disease-free interval of at least 2 years if they are known to be estrogen-receptor negative or a disease-free interval of at least 10 years if estrogen receptor status is unknown. These patients are being randomized to receive either ERT or no hormonal intervention, and it is expected that results from this study will better define the safety of HRT among breast cancer survivors.

HRT and Mammography

It is also worthwhile noting that women receiving HRT are likely to develop increases in breast density that may limit the sensitivity of mammography. It has been proposed that these women discontinue hormones for some period of time prior to undergoing mammographic imaging, but there is no published data to support the efficacy of this maneuver.

Laya et al. [64] reported a study of 8,779 postmenopausal women from Washington state and found that ERT was associated with a relative risk of 1.33 for a false-positive mammogram and 5.23 for a false-negative mammogram.

Alternatives to HR

The unresolved questions regarding the safety of ERT have prompted extensive research into alternative therapies for postmenopausal sequelae. These alternative regimens can be grossly categorized by target symptoms. Because of overlapping effects, the selective estrogen receptor modulators (SERMs) are discussed separately.

For osteoporosis, the options include bisphosphonates, supplemental calcium, vitamin D therapy, and calcitonin. Anabolic agents have been suggested but do not appear to have a significant effect.

Bisphosphonates are agents that reverse osteoporosis by inhibition of bone osteoclasts and they have a history of use in treating hypercalcemia for malignancy. Etidronate was an early bisphosphonate marketed for treating osteoporosis; however, its use has been limited osteomalacia may result from its inhibition of bone formation [65]. Alendronate, a second-generation bisphosphonate, was recently reviewed in the *New England Journal of Medicine* [66] and was found to have an efficacy approaching that of ERT in decreasing the clinical sequelae of osteoporosis, without the concerns regarding osteomalacia. Oral clodronate has been found to significantly reduce loss of bone mineral density in a group of breast cancer patients [67].

Calcium and vitamin D supplementation are well known to reduce the rate of bone loss [65, 68] and their routine use for all adults has been recommended. Calcitonin is another bone-antiresorptive agent; it is available in an injectable form for subcutaneous use or as a nasal inhalant. However, data on its ability to prevent fractures are lacking.

For vasomotor symptoms, clonidine, Bellargal, and

methyldopa are the most commonly prescribed alternatives to HRT; all, however, can be associated with significant adverse effects. Clonidine may cause fatigue, headache, and dizziness; bellergal can sedate; and the addictive potential of the phenobarbitol component may be unacceptable to many patients.

Phytoestrogens are chiefly derived from soybean products and papaya and have been associated with the decreased incidence of postmenopausal vasomotor symptoms among populations that typically consume diets enriched by these products [69]. Phytoestrogens have been shown also to have a favorable impact on serum lipid profile [70].

The SERM agents include tamoxifen, raloxifene, droloxifene, and idoxifene. Tamoxifen and raloxifene have been the most extensively investigated. The triphenylethyline tamoxifen has been shown to decrease serum cholesterol [71]; it also has the beneficial effects of increasing bone mineral density in a range comparable to estrogen therapy [72] and reducing risk of breast cancer in patients at high risk via its estrogen antagonist effect on breast tissue [73]. Unfortunately, the estrogen agonist effects of tamoxifen on uterine tissue cause an increased risk of endometrial cancer [74]. Other adverse effects of tamoxifen therapy include vasomotor symptoms, which are experienced by 25% of patients, risk of venous thrombosis, and retinopathies [75,76]. Interestingly, Lum et al. [77] have recently demonstrated that serum estrone and estradiol levels increase significantly after 2 years of tamoxifen therapy. The clinical significance of this data in terms of tamoxifen's estrogenic and chemopreventative properties is unclear at this time.

Raloxifene, a benzothiophene, appears to have the same types of favorable effects on bone and lipid metabolism as seen with tamoxifen, and because it behaves as an estrogen antagonist on uterine tissue, it does not cause endometrial hyperplasia [78]. Preliminary data suggests that raloxifene may be an effective chemopreventive agent for breast cancer [79], but longer follow-up is warranted.

TIMING OF SURGERY BASED ON THE MENSTRUAL CYCLE

The menstrual cycle comprises a first half (follicular phase) when estrogen levels are rising progressively and are mostly unopposed by progesterone and a second half (luteal phase) marked by a surge in luteinizing hormone, ovulation, and a progressive rise in progesterone levels.

For premenopausal patients with breast cancer, the controversy regarding the role of endogenous and exogenous hormones has led to speculation that timing of breast surgery in the context of menstrual cycle hormone level fluctuations may have an impact on outcome. This concept is predicated on the idea that surgical manipulation of a tumor results in release of micrometastases into the systemic circulation and that seeding of these micrometastases may be either inhibited or promoted depending on the hormonal environment. Some animal model and human model data support this concept.

TABLE IV. Timing of Breast Surgery: Studies Demonstrating a Protective Effect

Author, year	Number of patients	Protective days
Hrushesky et al., 1989 [82]	41	7–20
Veronesi et al., 1994 [83]	1,175	15–36
Senie et al., 1991 [84]	283	15–28
Marques and Franco, 1993 [85]	63	15–28
Badwe et al., 1991 [86]	249	0–2, 13–32
Saad et al., 1994 [87]	96	13–28
Spratt et al., 1993 [88]	40	7–20
Badwe et al., 1994 [89]	210	Prog $\geq$ 1.5 ng/ml

Studies have shown an increase in pulmonary metastases in mice undergoing tumor excision during an estrogen-dominant phase [80]. In humans, decreased natural killer cell and interleukin-2 production was demonstrated during the estrogen-dominant follicular phase of the menstrual cycle [80].

Hrushesky [81] was the first investigators to suggest that timing of surgery based on the menstrual cycle could impact survival, and this was based on his work with natural killer cell function [80]. To test this hypothesis, he performed a retrospective review of 41 patients with breast cancer for whom precise menstrual data was documented and correlated this information with dates of definitive surgery and relapse/survival data. In this initial study, surgery during the peri- and postovulatory period of the menstrual cycle, presumably when progesterone levels are rising, appeared to correlate with lower rates of breast cancer relapse. Several studies [82–89] since that time have demonstrated that the progesterone-dominant phase of the cycle correlates with some improvement in survival. The results of these studies are summarized in Table IV.

However, there is substantial published data that refutes these findings. One recent study by Chang et al. [90] from the Mayo Clinic found the earliest segment of the menstrual cycle, when estrogen is dominant and unopposed, to be associated with a survival benefit, although it was not statistically significant. Similarly, Sainsbury et al. [91] found the follicular phase to be protective. Powles et al. [92] found no correlation between timing of surgery based on the menstrual cycle and breast cancer survival. Most of the studies to date have been lacking in accurate serologic hormonal testing.

Two prospective clinical trials are currently underway to address these issues in a more scientific fashion [93] The European Institute of Oncology expects to recruit 3,150 patients, to be observed for 9 years; serum hormone levels will be determined pre- and postoperatively,

and transvaginal ultrasound will also be performed one day perioperatively to assess menstrual phase by uterine thickness. Oral contraceptive users will be included in this study. The National Cancer Institute anticipates 5-year follow-up of 880 patients (OC users excluded); serum hormone levels will be determined within 24 hours of surgery.

A recent study by Saad et al. [94] found variation in tumor expression of several genes associated with breast cancer proliferative activity based on timing of resection with the menstrual cycle. These results suggest that hormonal fluctuations may impact on the molecular biologic activity of breast tumors.

Although the data is intriguing, it should be kept in mind that this is an era of breast cancers being diagnosed and treated in multiple stages, frequently including preoperative chemotherapy. Therefore, results from many of these studies will not have a clear application to future patients.

NUTRITIONAL FACTORS

Dietary Fat

Dietary fat has for 50 years been recognized as a promoter of breast cancer in the animal model. Studies by Tannenbaum and Silverstone [95,96] demonstrated accelerated growth of mouse mammary tumors in association with diets rich in cottonseed oil. More recently, these findings have been reproduced using the DMBA-induced mammary tumor model [97], and dietary fat has been associated with an increased rate of mouse mammary metastases as well. Rose et al. [98] injected mice with cells from human breast cancer cell lines and, after several weeks of feeding isocaloric diets with varying proportions of linoleic acid, the investigators found an increase in the volume of pulmonary metastases among the mice whose diets were high in linoleic acid. Data from Ip et al. [99] indicate that such a promotional effect of dietary fatty acid is linear up to a certain point, beyond which the tumorigenic response appears to plateau. This concept of the threshold effect of dietary fat becomes important in the subsequent review of data on fat intake and cancer in cohort studies. Freedman et al. [100] performed a meta-analysis of 100 studies evaluating rat and mouse mammary tumorigenesis related to dietary fat, calories, and body weight. They found that dietary fat content enhanced mammary tumor development independently from the effects of caloric intake and weight.

Epidemiologic studies of populations and their fat intake relative to breast cancer incidence also support the concept of dietary fat being a promoter of the neoplastic process. In the United States, breast cancer has an incidence of over 100 per 100,000 women [101], and this population's diet consists of an estimated 40 to 45% of high-fat foods [102]. In contrast, the incidence of breast cancer is significantly lower in Japan (22 per 100,000), and the Japanese society historically has consumed a relatively low-fat diet (10 to 25% of high-fat foods) [102]. It has also been demonstrated that Asian immigrants to the United States who adopt American nutritional habits develop an increasing risk for breast cancer [103]. Prentice and Sheppard [104] looked at breast cancer incidence rates in several countries over two decades, and found that changes in incidence appeared to correlate with international variation in dietary fat consumption over time.

It appears that the type of dietary fat is at least as important as the quantity of fat consumed. As noted previously in the animal model studies, variation in dietary linoleic acid content correlated with changes in the rate of mouse mammary tumor growth and metastasis [98,99]. Rats fed oleic acid-enriched diets do not demonstrate these enhanced rates of neoplastic proliferation [105,106]. Linoleic acid, derived from safflower, sunflower, and corn oil, has been most convincingly associated with human tumorigenesis as well, and it has also been associated with decreased production of the tumor suppressor p53 protein product [102].

In contrast, oleic acid (derived from olive oil) and eicosapentaenoic acid (derived from fish oil) may actually be protective against breast cancer development. In countries where intake of these substances is high (such as Spain and Japan), there is a lower incidence of breast cancer [102]. The mechanism for these effects may be related to the finding that both oleic acid and eicosapentanoic acid interfere with the production of eicosanoids from linoleic acid; the n-6 eicosanoids (derived from linoleic acid) are associated with tumor growth and metastasis [102].

A review of 12 case-control studies of diet and breast cancer by Howe et al. [107] demonstrated a consistent and statistically significant association between saturated fat intake and breast cancer risk for postmenopausal women.

Prospective cohort studies such as the Framingham [108] and Tecumseh [109] studies, however, have not demonstrated a clear correlation between dietary fat intake and breast cancer incidence. The cohort studies are known to have significant limitations. Most of them rely on self-reporting of fat intake, and many people tend to underestimate dietary fat content. The second limitation is related to the concept mentioned previously that dietary fat promotes tumorigenesis via a threshold effect, as seen in animal models. Thus, a prospective study of a cohort of people from the same society eating a similar diet, which may exceed the threshold level, is unlikely to reveal any significant variation in cancer incidence. However, in the pooled analysis by Hunter et al. [110] of seven prospective studies performed in four different countries, even after adjusting for measurement error in fat intake determinations, significant variation in breast

cancer incidence based on dietary fat intake could not be identified. They, therefore, concluded that, "in the context of the Western lifestyle, lowering the total intake of fat in midlife is unlikely to reduce the risk of breast cancer substantially."

Several studies have also looked specifically at dietary fat in patients with a history of breast cancer, and increased fat intake has been associated with increased likelihood of axillary nodal positivity [111], higher relapse rates [112], and poorer survival [113]. Based upon this type of data, Chlebowski et al. [114] evaluated the feasibility of a dietary fat intake reduction program among 290 postmenopausal patients with breast cancer and found that significant and sustained lower fat consumption and weight loss could be achieved.

It has also been proposed that dietary fat may account in part for the higher breast cancer mortality rates seen in particular subsets of the American population, such as African Americans. This speculation is based on data that black patients with breast cancer tend to have a higher body mass index than do white patients. Coates et al. [115] prospectively followed 1,960 breast cancer patients from Georgia and found that higher body weight and poorer nutritional status (as measured by hemoglobin and serum albumin levels) were independently associated with a poorer survival rate of the black patients. Jones et al. [116] demonstrated severe obesity among black breast cancer patients was an independent feature of poor prognosis. If the correlation of dietary fat and body weight is accurate, then it is possible that dietary intervention may be partially successful in race-related disparity in breast cancer survival. There is some indirect evidence that this type of intervention may be effective. In a study reported by Woods et al. [117], healthy premenopausal black women were found to have significantly higher baseline serum hormone levels compared with white women, and dietary manipulation from a high-fat/low-fiber to a low-fat/high-fiber diet resulted in decreases in these serum hormone levels. Jones et al. [118] demonstrated similar results among a cohort of postmenopausal African-American women.

Dietary fat can also influence breast tissue density in a manner that suggests that it may be a useful marker in chemoprevention studies and dietary intervention models. In a study by Boyd et al. from the Canadian Diet and Breast Cancer Prevention Study Group [119], more than 800 patients (75% were premenopausal) with mammographically dense breasts were randomized to two groups. The control group continued to consume a usual high-fat diet, and the intervention study group was given a 15% fat diet. After 2 years of follow-up, there was a significant decrease in breast tissue density among the study group, even after accounting for weight loss. This data is particularly intriguing in light of evidence that breast density may be a risk factor for breast cancer [120], and it suggests that mammography may be useful as a surrogate marker for the success of dietary intervention programs.

Dietary Fiber

The possible impact of a high-fiber diet on breast cancer risk was reviewed by Stoll [121]. Dietary fiber has been purported to reduce breast cancer growth by decreasing circulating levels of bioactive estrogens. One mechanism explaining this effect is reduced enterohepatic recirculation of estrogen. Another possible mechanism is that fiber-associated substances that can be converted to weak estrogens in the gastrointestinal tract may then compete with estradiol for target binding sites. Another indirect effect may be mediated by the favorable influence of fiber on insulin resistance and hyperinsulinemia, because insulin is a known growth factor for human mammary cancer cells.

Vitamin D

In vitro cell culture studies demonstrated that 1α,25 dihydroxyvitamin D_3 suppresses breast cancer growth [122]; however, clinical studies are limited by the hypercalcemic effects of vitamin D. Therefore, vitamin D analogs are now being developed as potential chemopreventive and therapeutic agents. One such analogue, 1α-hydroxyvitamin D_5, has demonstrated the ability to inhibit DMBA-induced preneoplastic lesions in mice [123] and another, 22-Oxa-1,25-dihydroxyvitamin D_3, has been shown to inhibit human breast cancer growth in vitro and in a mouse model [124].

Phytoestrogens

As noted previously, phytoestrogens may have significant clinical applications as an alternative to ERT for postmenopausal symptoms, and their utility for chemoprevention is currently being investigated. Isoflavanoids derived from soy products have been found in vitro to have antiangiogenic properties [125], and epidemiologic data reveal that in populations such as the Japanese and Indonesians who consume soy-rich diets, there is a correspondingly lower incidence of breast cancer [126].

CONCLUSIONS

The data regarding exogenous hormone use and breast cancer risk remain controversial. For most women, there is probably no significant increased risk associated with oral contraceptives (especially if use is limited to less than 5 years), and hormone replacement therapy for postmenopausal women will clearly ameliorate some of the disease states associated with estrogen deficiency, namely osteoporosis and atherosclerotic heart disease. These beneficial effects are most pronounced for women with preexisting risk factors for coronary artery disease, and they must be weighed against the possible increase in

breast cancer morbidity after prolonged use (more than 10 years). It is premature to consider routine timing of surgery based on the menstrual cycle for premenopausal women. However, clinicians are awaiting the results of prospective randomized trials, so as to incorporate the findings into current multistage and multimodality approaches to breast cancer. A healthy lifestyle and low-fat, high-fiber diet are sensible for overall well-being and should be recommended to women before, during, and after systemic breast cancer therapy.

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